[0014] Figures 3A-3D show the anti-tumor efficacy of monotherapy of anti-GITR or anti-PD-1 antibodies alone (Figs 3C-3D), compared to co-administration of both antibodies (Fig. 3A) in the CT26 tumor model (n=10/group).

[0015] Figures 4A-4D show the effect of anti-GITR and anti PD-1 antibodies dosed alone or with concurrent administration of both antibodies on the anti-tumor response of mice implanted with the MB49 cell line (n=10/group). Treatment was commenced when tumors reached 85-122 mm^3.

[0016] Figures 5A-5B show the dose dependent effect of the combination of anti-GITR (MK-4166) and anti-PD-1 (MK-3475) on Tregs (Fig. 5A) and Treg:CD8 cell ratio (Fig. 5B) in a mixed lymphocyte reaction (MLR).

[0017] Figure 6 shows that incubation with a combination of MK-4166 and MK-3475 results in reduced suppressive activity of Tregs in an MLR.

SUMMARY

[0018] The present disclosure meets these needs in the art and more by providing a method of treating a tumor in a patient comprising administering to the patient a PD-1 antagonist and a GITR agonist, wherein the PD-1 antagonist and GITR agonist are administered simultaneously or sequentially. In certain embodiments, the PD-1 antagonist is an antibody or antigen binding fragment thereof, that binds PD-1 or PD-L1; and the GITR agonist is an antibody or antigen binding fragment thereof that binds GITR. The GITR agonist and PD-1 or PD-L1 antagonist binds to the human proteins. The antibody or binding fragment thereof is humanized or fully human.

[0018a] In one aspect, there is provided a combination of a PD-1 antagonist, which is MK-3475, and a GITR agonist, which is an antibody or antigen-binding fragment that binds GITR comprising: a light chain immunoglobulin variable region that comprises CDR-L1, CDR-L2 and CDR-L3 of the light chain immunoglobulin variable region comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q; and a heavy chain immunoglobulin variable region that comprises CDR-H1, CDR-H2 and CDR-H3 of the heavy chain immunoglobulin variable region comprising the amino acid sequence set forth in SEQ ID NO: 81; for use in treating a tumor in a patient, wherein the PD-1 antagonist and GITR agonist are to be administered simultaneously or sequentially.

[0019] In further embodiments, the PD-1 antagonist is selected from the group consisting of BMS-936558, MK-3475, and MPDL3280A; and GITR agonist is selected from the group consisting of an antibody having at least one CDR of SEQ ID NOs: 1 - 66; TRX518; and TRX385. The GITR agonist can be an antibody having: a heavy chain CDR1 of SEQ ID NOs: 1-11, CDR2 of SEQ ID NOs: 12-22, and CDR3 of SEQ ID NOs: 23-33; and/or a light chain CDR1 of SEQ ID NOs: 34-44, CDR2 of SEQ ID NOs: 45-55, and CDR3 of SEQ ID NOs: 56-66. In yet a further embodiment, the GITR agonist is an antibody having: a variable heavy chain of SEQ ID NOs: 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, and 87; and/or a variable light chain of SEQ ID NO: 68, 70, 72, 74, 76, 78, 80, 82, 84, 86, and 88.

[0020] The present disclosure also contemplates that the PD-1 antagonist and GITR agonist are administered concurrently at least one time. In certain embodiments, the PD-1 antagonist and GITR agonist are administered concurrently at least 2 times. In certain

[0023] The present disclosure provides a pharmaceutical composition comprising a PD-1 antagonist and a GITR agonist. In another aspect, there is provided a pharmaceutical combination comprising a PD-1 antagonist and a GITR agonist, wherein: a) the PD-1 antagonist is MK-3475; and b) the GITR agonist is an antibody or antige-binding fragment that comprises: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q; and CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81.

[0023a] Also provided is the use of a PD-1 antagonist in combination with a GITR agonist to treat an advanced stage tumor. In another aspect, there is provided use of a PD-1 antagonist, which is MK-3475, and a GITR agonist which is an antibody or antigen-binding fragment that comprises: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q; and CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81, in the manufacture of a medicament for the treatment of a tumor in a patient, wherein the PD-1 antagonist and GITR agonist are for administration simultaneously or sequentially. In another aspect, there is provided use of a PD-1 antagonist and a GITR agonist in the manufacture of a medicament for the treatment of an advanced stage tumor, wherein: a) the PD-1 antagonist is MK-3475; and b) the GITR agonist is sa humanized antibody comprising: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q; and CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81.

CLAIMS

WHAT IS CLAIMED IS:

1. A combination of a PD-1 antagonist, which is MK-3475, and a GITR agonist, which is an antibody or antigen-binding fragment that binds GITR comprising: a light chain immunoglobulin variable region that comprises CDR-L1, CDR-L2 and CDR-L3 of the light chain immunoglobulin variable region comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q;
and

a heavy chain immunoglobulin variable region that comprises CDR-H1, CDR-H2 and CDR-H3 of the heavy chain immunoglobulin variable region comprising the amino acid sequence set forth in SEQ ID NO: 81; for use in treating a tumor in a patient, wherein the PD-1 antagonist and GITR agonist are to be administered simultaneously or sequentially.

2. The combination of claim 1, wherein
the GITR agonist is an antibody that binds GITR.

3. The combination of claim 2, wherein the GITR agonist is a humanized antibody that binds to GITR and the patient is human.

4. The combination of claim 1, wherein the PD-1 antagonist and GITR agonist are to be administered simultaneously at least one time.

5. The combination of claim 1, wherein the PD-1 antagonist and GITR agonist are to be administered simultaneously at least 2 times.

6. The combination of claim 1, wherein the tumor is an advanced stage tumor.

7. The combination of claim 6, wherein the advanced stage tumor is selected from the group consisting of squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer, hepatic carcinoma, hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, myeloma, multiple myeloma, salivary gland carcinoma, kidney cancer, renal cell carcinoma, Wilms' tumors, basal cell carcinoma, melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, and esophageal cancer.

8. A pharmaceutical combination comprising a PD-1 antagonist and a GITR agonist, wherein:

a) the PD-1 antagonist is MK-3475; and

b) the GITR agonist is an antibody or antigen-binding fragment that comprises: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q; and

CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81.

9. Use of a PD-1 antagonist, which is MK-3475, and a GITR agonist which is an antibody or antigen-binding fragment that comprises: CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q; and

CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81, in the manufacture of a medicament for the treatment of a tumor in a patient, wherein the PD-1 antagonist and GITR agonist are for administration simultaneously or sequentially.

10. The use of claim 9, wherein

the GITR agonist is an antibody that binds GITR.

11. The use of claim 10, wherein the GITR agonist is a humanized antibody and the patient is human.

12. The use of claim 9, wherein the PD-1 antagonist and GITR agonist for administration simultaneously at least one time.

13. The use of claim 9, wherein the PD-1 antagonist and GITR agonist are for administration simultaneously at least 2 times.

14. The use of claim 9, wherein the tumor is an advanced stage tumor.

15. The use of claim 14, wherein the advanced stage tumor is selected from the group consisting of squamous cell cancer, small-cell lung cancer, non-small cell lung cancer, gastrointestinal cancer, pancreatic cancer, glioblastoma, glioma, cervical cancer, ovarian cancer, liver cancer, hepatic carcinoma, hepatoma, bladder cancer, breast cancer, colon cancer, colorectal cancer, endometrial carcinoma, myeloma, multiple myeloma, salivary gland carcinoma, kidney cancer, renal cell carcinoma, Wilms' tumors, basal cell carcinoma,

melanoma, prostate cancer, vulval cancer, thyroid cancer, testicular cancer, and esophageal cancer.

16. Use of a PD-1 antagonist and a GITR agonist in the manufacture of a medicament for the treatment of an advanced stage tumor, wherein:

a) the PD-1 antagonist is MK-3475; and

b) the GITR agonist is a humanized antibody comprising:

CDR-L1, CDR-L2 and CDR-L3 of the variable light chain comprising the amino acid sequence set forth in SEQ ID NO: 82 wherein amino acid 31 is Q and amino acid 57 is Q; and

CDR-H1, CDR-H2 and CDR-H3 of the variable heavy chain comprising the amino acid sequence set forth in SEQ ID NO: 81.